



Heriot-Watt University
Research Gateway

Polyphenols as new leads in drug discovery

Citation for published version:

Dos Santos, CN, Menezes, R & Stewart, D 2018, 'Polyphenols as new leads in drug discovery: Biological activity and mechanisms', *Current Pharmaceutical Design*, vol. 24, no. 19, pp. 2041-2042.
<https://doi.org/10.2174/138161282419180924094610>

Digital Object Identifier (DOI):

[10.2174/138161282419180924094610](https://doi.org/10.2174/138161282419180924094610)

Link:

[Link to publication record in Heriot-Watt Research Portal](#)

Document Version:

Peer reviewed version

Published In:

Current Pharmaceutical Design

General rights

Copyright for the publications made accessible via Heriot-Watt Research Portal is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy

Heriot-Watt University has made every reasonable effort to ensure that the content in Heriot-Watt Research Portal complies with UK legislation. If you believe that the public display of this file breaches copyright please contact open.access@hw.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.

Editorial

Guest Editors: Claudia Nunes dos Santos, Regina Menezes and Derek Stewart

Plants are natural reservoirs of a diversity of compounds, many of which have pharmacological/nutraceutical activities towards a variety of diseases. One important class of plant bioactive compounds is polyphenols. The term phenol is used to describe a structure with at least one aromatic ring containing one or more hydroxyl groups attached and the flavonoids, with several aromatic rings, represent a well-known subgroup of bioactive polyphenols. Other compounds, including hydroxycinnamates and phenolic acids, with only one phenolic ring are also referred to as polyphenols. These phytochemicals occur naturally in plants and epidemiological, pre-clinical and clinical studies have shown their importance for human health as they reduce the incidence and prevalence of cardiovascular diseases, cancer, diabetes, inflammation and age-related disorders. Modern pharmacopeia has received significant input from natural small molecules (such as polyphenols); however, the process of identifying novel bioactive compounds from biological sources has been a central challenge in the discovery of natural products. Moreover the exploitation of polyphenols as sources of molecules with pharmacological/nutraceutical interest depends on effective methods for compounds extraction to be further tested as regard their chemical and biological activities. Additionally, the use of fractionation procedures coordinated with bioactivity/antimicrobial screenings – bio-guided fractionation – is required for the identification of single compounds with therapeutic potential. Once identified, the pharmacokinetics and *modus operandi* of compounds need to be gathered to support the rational design and synthesis of medicinal chemistry derivatives. Alternatively, large-scale production of potential bioactive polyphenols can be achieved by means of synthetic biology. At last, technologies of controlled delivery must ensure that the compounds are carried to the site of action. The ultimate goal of this pipeline is to discover and make available to society therapeutic alternatives for chronic diseases including cancer, neurodegenerative, cardiovascular, and metabolic diseases.

The thematic issue is a journey in the field of polyphenols as bioactive compounds for health, exploring the current strategies for identification, characterization, improvement and production of these protective molecules.

Foito *et al.* described the state of art methodologies used for structural elucidation and annotation of novel bioactive compounds. An overview of the metabolomics toolbox available, from hyphenated mass spectrometry (MS) and nuclear magnetic resonance (NMR)-based analytical technologies, is described alongside with technical developments in instrumentation and data processing. In addition, the authors explore the importance of the integration of these tools in the bioprospection and drug

discovery workflows. Overall, the review assesses the huge potential of metabolomics for application in the process of drug/bioactive discovery from plants.

The degeneration of neurons in specific brain regions is one of the main causes of chronic neurodegenerative diseases (NDs) and the formation of aggregates of misfolded proteins has been considered a hallmark underlying the pathophysiology of these diseases. Kostelidou *et al.* discussed the available microbial (bacteria and yeast) genetic screens and selection systems targeting NDs-associated protein misfolding, which facilitate the identification of cellular factors and disease processes as well as the discovery of synthetic and natural compounds with protective activities.

As the simplest eukaryotic organism yeast shares fundamental biological processes with mammalian cells, including some processes associated with human diseases. This feature allows the use of *Saccharomyces cerevisiae* as test-tubes to decipher the molecular mechanisms underlying disease pathology as well as to accelerate the discover of protective molecules. In addition, mammalian cell models have been widely used in polyphenol research to identify/validate polyphenol bioactivity for chronic diseases. Rosado-Ramos *et al.* reviewed the use of eukaryotic cell models of NDs and their contribution for the identification of novel bioactivities as well as the benefits and limitations of their use as tools in the search for bioactive polyphenols.

The use of the nematode *Caenorhabditis elegans* has been largely explored in aging research and, more recently, to investigate the multi-faceted properties of polyphenols as protective candidates for aging-related conditions. In this issue, Papaevgeniou & Chondrogianni compiled the studies addressing the anti-aging and neuroprotective potential of polyphenols using *C. elegans* as multicellular model organism.

Epidemiological evidence suggests that polyphenol-rich diets lower the risk of certain cancers whereas epidemiological, *in vitro*, *in vivo* and clinical studies point to the fact that natural polyphenols can be potentially used for the prevention and treatment of cancer. Momtazi *et al.* reviewed the effects of curcumin on nasopharyngeal cancer, a rare type of head and neck cancer that is mainly treated by radiotherapy. Curcumin is a well-established polyphenol with chemosensitizing, chemotherapeutic and radiosensitizing effects and its chemopreventive potential has been studied in a variety of cancers. The authors highlight recent studies showing that curcumin has therapeutic and radio-sensitizing effects on nasopharyngeal cancer cells as well their mechanism of action. Overall, the potential of using curcumin as co-adjuvant of chemotherapy without secondary systemic toxic effects in humans is discussed. Besides cancer, the therapeutic benefits of curcumin have also been described for inflammatory processes, immunological disorders, diabetes, and oxidative stress. The molecule has a unique molecular structure that easily interacts with biomolecules like protein and enzymes,

thereby impacting their function/activity. Hatamipour *et al.* discussed the underlying mechanisms responsible for those chemical interactions of curcumin.

The cardiovascular system is another field where the protective activity of polyphenols is well documented, particularly for atherosclerosis, hypertension, myocardial infarction, anthracyclin-induced cardiomyopathy, angiogenesis and heart failure. Santos *et al.* reviewed the knowledge of the main pharmacological effects and mechanisms of cardioprotection mediated by polyphenols in the heart and vessels obtained, from *in vitro*, animal and human studies.

Hydroxytyrosol, and its derivatives from virgin olive oil, are important phytochemicals with proved activity for lifestyle-associated pathologies such as cancer, cardiovascular and neurodegenerative diseases, as indicated by epidemiological evidences. Hazas *et al.* reviewed its natural occurrence, metabolic fate and bioavailability as well its health beneficial effects together with newest perspectives on the mechanisms of action based on *in vitro* and animal studies. The authors concluded that hydroxytyrosol, and its derivatives, could have potential clinical use in cardiovascular diseases. However, more epidemiological data is needed to evaluate their preventive effects for NDs and cancer.

Diabetes is a chronic metabolic disorder associated with several comorbidities, including diabetic retinopathy (DR), and increased oxidative stress in the retina seems to trigger the damage of both neuronal and vascular cells. Ola *et al.* reviewed the evidence pointing out the potential metabolic sources and pathways related to the increase of oxidative stress in DR and the role of dietary flavonoids, particularly flavonones, flavanols, flavonols, isoflavones, flavones and anthocyanins, in the modulation of redox homeostasis in diabetic retina.

Given the myriad of bioactivities described for polyphenols, these molecules have emerged as lead compounds for the design and synthesis of improved molecules with therapeutic application for several diseases. Almeida *et al.* described how organic synthesis has been essential for the development of these new analogues, providing a wide range of structural modifications for structure-activity relationship studies and improving/modulating the biological activity of promising compounds.

The studies reviewed in this issue unequivocally show the potential of polyphenols to modify pathological processes associated with chronic diseases and the efforts of organic chemistry to develop novel molecules with improved activity. Nonetheless, the majority of these compounds are still obtained from plant material by means of costly and inefficient extraction procedures. Dudnik *et al.* reviewed the use of metabolic engineering and microbial cell factories (*Escherichia coli*, *S. cerevisiae*, *Corynebacterium glutamicum* and *Lactococcus lactis*) as emerging alternatives allowing efficient and sustainable production of protective polyphenols.

Overall, eleven outstanding international experts were invited to contribute to this

thematic issue and to share their opinions, with perspectives of polyphenol research for the advance in therapy for chronic diseases. We hope the multidisciplinary topics discussed with the theme issue will promote further discussion among pharmaceutical/nutraceutical industry and researchers.